CLAIMS

1. A binding partner for the TSH receptor, which binding partner comprises, or is derived from, a human monoclonal or recombinant antibody, or one or more fragments thereof, reactive with the TSH receptor.

2. A binding partner for the TSH receptor, which binding partner comprises, or is derived from, a human monoclonal antibody, or one or more fragments thereof, reactive with the TSH receptor.

3. A binding partner for the TSH receptor, which binding partner comprises, or is derived from, a human recombinant antibody, or one or more fragments thereof, reactive with the TSH receptor.

4. A human monoclonal antibody, or one or more fragments thereof, reactive with the TSH receptor.

5. A human recombinant antibody, or one or more fragments thereof, reactive with the TSH receptor.

6. A binding partner for the TSH receptor, which binding partner comprises, or is derived from, one or more fragments of a human recombinant antibody reactive with the TSH receptor.

7. A binding partner for the TSH receptor according to any of claims 1 to 6, which has the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor.

8. A binding partner for the TSH receptor according to any of claims 1 to 6, which has the characteristics of patient serum TSH receptor autoantibodies with respect to stimulation of cAMP production by cells expressing the TSH receptor.

9. A binding partner for the TSH receptor according to any of claims 1 to 6, which has the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor and with respect to stimulation of cAMP production by cells expressing the TSH receptor.

10. A binding partner according to any of claims 1 to 9, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

11. A binding partner according to claim 10, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

12. A binding partner according to any of claims 1 to 11, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

13. A binding partner according to claim 12, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

14. A binding partner according to any of claims 1 to 13, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

15. A binding partner according to claim 14, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

16. A binding partner according to any of claims 1 to 15, which comprises or is derived from one or more fragments of a monoclonal or recombinant antibody reactive with the TSH receptor, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg.

17. A binding partner according to claim 16, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg.

18. A binding partner according to any of claims 1 to 17, which comprises or is derived from one or more fragments of a monoclonal or recombinant antibody reactive with the TSH receptor, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 50 units of International Standard NIBSC 90/672 per mg.

19. A binding partner according to claim 18, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 400 units of International Standard NIBSC 90/672 per mg.

20. A binding partner according to any of claims 1 to 19, which comprises or is derived from one or more fragments of a monoclonal or recombinant antibody reactive with the TSH receptor, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 50 units of International Standard NIBSC 90/672 per mg.

21. A binding partner according to claim 20, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 400 units of International Standard NIBSC 90/672 per mg.

22. A binding partner for the TSH receptor which comprises an antibody V_H domain selected from the group consisting of a V_H domain as shown in SEQ ID NO. 1 and a V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 3 and SEQ ID NO. 4.

23. A binding partner for the TSH receptor which comprises an antibody V_H domain as shown in SEQ ID NO. 1.

24. A binding partner for the TSH receptor which comprises an antibody V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 3 and SEQ ID NO. 4.

25. A binding partner for the TSH receptor which comprises:

an antibody V_H domain selected from the group consisting of:

a V_H domain as shown in SEQ ID NO. 1 and a V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 3 and SEQ ID NO. 4; and / or

an antibody V_L domain selected from the group consisting of:

a V_L domain as shown in SEQ ID NO. 6 and a V_L domain comprising one or more V_L CDRs with an amino acid sequence selected from SEQ ID NO. 7, SEQ ID NO. 8 and SEQ ID NO. 9.

26. A binding partner according to claim 25, comprising an antibody V_H domain as shown in SEQ ID NO. 1 paired with an antibody V_L domain as shown in SEQ ID NO. 6 to provide an antibody binding site, comprising both said V_H and V_L domains for the TSH receptor.

27. A binding partner according to claim 25, which comprises:

an antibody V_H domain comprising:

a V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 3 and SEQ ID NO. 4; and / or

an antibody V_L domain comprising:

a V_L domain comprising one or more V_L CDRs with an amino acid sequence selected from SEQ ID NO. 7, SEQ ID NO. 8 and SEQ ID NO. 9.

28. A further binding partner capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor

according to any of claims 1 to 27, which further binding partner does not comprise TSH.

29. A further binding partner according to claim 28, which comprises a further antibody having a binding site for an epitope region of the TSH receptor and which competes for binding to the TSH receptor with a binding partner according to any of claims 1 to 27.

30. A further binding partner according to claim 29, which comprises, or is derived from, a human monoclonal or recombinant antibody, or one or more fragments thereof, reactive with the TSH receptor.

31. A further binding partner according to claim 29, which comprises, or is derived from, a mouse monoclonal or recombinant antibody, or one or more fragments thereof, reactive with the TSH receptor.

32. A further binding partner according to any of claims 28 to 31, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

33. A further binding partner according to claim 32, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

34. A further binding partner according to any of claims 28 to 33, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

35. A further binding partner according to claim 34, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

36. A further binding partner according to any of claims 28 to 35, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

37. A further binding partner according to claim 36, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

38. A further binding partner capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor according to any of claims 1 to 27, which further binding partner comprises an antibody V_H domain as shown in SEQ ID NO. 19.

39. A further binding partner capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor according to any of claims 1 to 27, which further binding partner comprises an antibody V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 20, SEQ ID NO. 21 and SEQ ID NO. 22.

40. A further binding partner capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor according to any of claims 1 to 27, which further binding partner comprises:

an antibody V_H domain selected from the group consisting of:

a V_H domain as shown in SEQ ID NO. 19 and a V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 20, SEQ ID NO. 21 and SEQ ID NO. 22; and / or

an antibody V_L domain selected from the group consisting of:

a V_L domain as shown in SEQ ID NO. 24 and a V_L domain comprising one or more V_L CDRs with an amino acid sequence selected from SEQ ID NO. 25, SEQ ID NO. 26 and SEQ ID NO. 27.

41. A further binding partner according to claim 40, which comprises an antibody V_H domain as shown in SEQ ID NO. 19 paired with an antibody V_L domain as shown in SEQ ID NO. 24 to provide an antibody binding site, comprising both these V_H and V_L domains for the TSH receptor.

42. A further binding partner according to claim 40, which comprises:

an antibody V_H domain comprising:

a V_H domain comprising one or more V_H CDRs with an amino acid sequence selected from SEQ ID NO. 20, SEQ ID NO. 21 and SEQ ID NO. 22; and / or

an antibody V_L domain comprising:

a V_L domain comprising one or more V_L CDRs with an amino acid sequence selected from SEQ ID NO. 25, SEQ ID NO. 26 and SEQ ID NO. 27.

43. A polynucleotide comprising:

(i) a nucleotide sequence as shown in SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17 or SEQ ID NO. 18, encoding an amino acid sequence of an antibody V_H domain, V_L domain, or CDR, as shown in SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8 or SEQ ID NO. 9;

(ii) a nucleotide sequence encoding a binding partner for the TSH receptor according to any of claims 22 to 27, or encoding an amino acid sequence of an antibody V_H domain, V_L domain, or CDR, of a binding partner for the TSH receptor according to any of claims 22 to 27;

(iii) a nucleotide sequence differing from any sequence of (i) in codon sequence due to the degeneracy of the genetic code;

(iv) a nucleotide sequence comprising an allelic variation of any sequence of (i);

(v) a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), or (iv) and in particular a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), (iv) or (v) and encoding a Fab fragment, a Fd fragment, a Fv fragment, a dAb fragment, an isolated CDR region, F(ab')2 fragments or a scFv fragment, of a binding partner for the TSH receptor according to any of claims 22 to 27;

(vi) a nucleotide sequence differing from the any sequence of (i) due to mutation, deletion or substitution of a nucleotide base and encoding a binding partner for the TSH receptor according to any of claims 22 to 27, or encoding

an amino acid sequence of an antibody V_H domain, V_L domain, or CDR, of a binding partner for the TSH receptor according to any of claims 22 to 27.

44. A polynucleotide comprising:

(i) a nucleotide sequence as shown in SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36 or SEQ ID NO. 37, encoding an amino acid sequence of an antibody V_H domain, V_L domain, or CDR, as shown in SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26 or SEQ ID NO. 27;

(ii) a nucleotide sequence encoding a further binding partner for the TSH receptor according to any of claims 38 to 42, or encoding an amino acid sequence of an antibody V_H domain, V_L domain, or CDR, of a further binding partner for the TSH receptor according to any of claims 38 to 42;

(iii) a nucleotide sequence differing from any sequence of (i) in codon sequence due to the degeneracy of the genetic code;

(iv) a nucleotide sequence comprising an allelic variation of any sequence of (i);

(v) a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), or (iv) and in particular a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), (iv) or (v) and encoding a Fab fragment, a Fd fragment, a Fv fragment, a dAb fragment, an isolated CDR region, F(ab')2 fragments or a scFv fragment, of a further binding partner according to any of claims 38 to 42;

(vi) a nucleotide sequence differing from the any sequence of (i) due to mutation, deletion or substitution of a nucleotide base and encoding a further binding partner according to any of claims 38 to 42, or encoding an amino

acid sequence of an antibody V_H domain, V_L domain, or CDR, of a further binding partner for the TSH receptor according to any of claims 38 to 42.

45. A biologically functional vector system which carries a polynucleotide according to claim 43 or 44 and which is capable of introducing the polynucleotide into the genome of a host organism.

46. A host cell which is transformed with a polynucleotide according to claim 43 or 44.

47. A process of providing a human monoclonal antibody to the TSH receptor, which process comprises:

(i) providing a source of lymphocytes from a subject, which subject has TSH receptor antibody activity of greater than about 0.04 units of NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor;

(ii) isolating lymphocytes from said lymphocyte source of (i);

(iii) immortalising the isolated lymphocytes; and

(iv) cloning the immortalised lymphocytes so as to produce an immortalised colony secreting a human monoclonal antibody to the TSH receptor according to any of claims 1, 2, 4, and 7 to 27.

48. A process of providing a human monoclonal antibody to the TSH receptor, which comprises:

(i) providing a source of lymphocytes from a subject, which subject has TSH receptor antibody activity of greater than about 0.1 units of NIBSC 90/672 per mL of serum with respect to stimulatory activity of cAMP production by cells expressing the TSH receptor;

(ii) isolating lymphocytes from said lymphocyte source of (i);

(iii) immortalising the isolated lymphocytes; and

(iv) cloning the immortalised lymphocytes so as to produce an immortalised colony secreting a human monoclonal antibody to the TSH receptor according to any of claims 1, 2, 4, and 7 to 27.

49. A process according to claim 47 or 48, which comprises isolating lymphocytes from peripheral blood, thyroid tissue, spleen tissue, lymph nodes or bone marrow.

50. A process according to claim 47, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels of greater than about 0.1 units of NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

51. A process according to claim 50, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels of greater than about 0.2 units of NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

52. A process according to claim 51, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels in the range of about 0.3 to 0.5 units of NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

53. A process according to claim 48, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels of greater than about 0.3 units of NIBSC 90/672 per mL of serum with respect to stimulatory activity of cAMP production by cells expressing the TSH receptor.

54. A process according to claim 53, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels of

greater than about 0.5 units of NIBSC 90/672 per mL of serum with respect to stimulatory activity of cAMP production by cells expressing the TSH receptor.

55. A process according to claim 54, wherein the source of lymphocytes is characterised as being obtained from a subject having TSH receptor antibody levels in the range of about 0.5 to 1.0 units of NIBSC 90/672 per mL of serum with respect to stimulatory activity of cAMP production by cells expressing the TSH receptor.

56. A process according to any of claims 47 to 55, which comprises infecting the isolated lymphocytes with Epstein Barr virus, and the thus immortalised lymphocytes are fused with a mouse or human cell line.

57. A process of preparing a human recombinant antibody, or one or more fragments thereof, to the TSH receptor, which process comprises cloning and expression of a human monoclonal antibody to the TSH receptor, or one or more fragments derived therefrom.

58. A process according to claim 57, wherein said human monoclonal antibody to the TSH receptor is prepared by a process according to any of claims 47 to 56.

59. A human monoclonal or recombinant antibody to the TSH receptor, as respectively obtained by a process according to any of claims 47 to 58.

60. A human monoclonal or recombinant antibody according to claim 59, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

61. A human monoclonal or recombinant antibody according to claim 60, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

62. A human monoclonal or recombinant antibody according to any of claims 59 to 61, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

63. A human monoclonal or recombinant antibody according to claim 62, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg, or one or more fragments thereof.

64. A human monoclonal or recombinant antibody according to any of claims 59 to 63, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 15 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

65. A human monoclonal or recombinant antibody according to claim 64, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 120 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg;

or one or more fragments thereof.

66. One or more fragments of a human monoclonal or recombinant antibody according to any of claims 59 to 65, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg.

67. One or more fragments according to claim 66, characterised by an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg.

68. One or more fragments of a human monoclonal or recombinant antibody according to any of claims 59 to 67, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 50 units of International Standard NIBSC 90/672 per mg.

69. One or more fragments according to claim 68, characterised by a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 400 units of International Standard NIBSC 90/672 per mg.

70. One or more fragments according to any of claims 66 to 69, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 30 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 50 units of International Standard NIBSC 90/672 per mg.

71. One or more fragments according to claim 70, characterised by:

(i) an inhibitory activity with respect to TSH binding to the TSH receptor, of at least about 240 units of International Standard NIBSC 90/672 per mg; and

(ii) a stimulatory activity with respect to cAMP production by cells expressing the TSH receptor, of at least about 400 units of International Standard NIBSC 90/672 per mg.

72. A process according to any of claims 47 to 58, which further comprises a further process stage whereby the obtained human monoclonal or recombinant antibody is subjected to further processing techniques so as to obtain a further binding partner according to any of claims 28 to 37.

73. A further binding partner according to any of claims 28 to 37, obtained by a process according to claim 72.

74. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of said binding pair comprises a binding region with which said binding partner or further binding partner interacts;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an

indication of the presence of said autoantibodies to the TSH receptor in said sample.

75. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of said binding pair comprises a binding region with which said binding partner or further binding partner interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

76. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a human or non-human polyclonal antibody to the TSH receptor and a second molecule of said binding pair comprises a binding region with which said polyclonal antibody interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said polyclonal antibody; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

77. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises TSH or one or more variants, analogs, derivatives or fragments thereof, and a second molecule of said binding pair comprises a binding region with which said TSH or one or more variants, analogs, derivatives or fragments thereof interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample

essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said TSH or one or more variants, analogs, derivatives or fragments thereof; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

78. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner for the TSH receptor which has an affinity for the TSH receptor of 10^{10}molar^{-1} or greater and a second molecule of said binding pair comprises a binding region with which said binding partner interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner for the TSH; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

79. Use of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, for detecting autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, wherein the interaction of said binding partner or further binding partner with the TSH receptor is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

80. Use of a human or non-human polyclonal antibody to the TSH receptor, for detecting autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, wherein the interaction of said polyclonal antibody with the TSH receptor is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

81. Use of TSH or one or more variants, analogs, derivatives or fragments thereof, for detecting autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, wherein the interaction of said TSH or one or more variants, analogs, derivatives or fragments thereof with the TSH receptor is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

82. Use of a binding partner for the TSH receptor which has an affinity for the TSH receptor of 10^{10}molar^{-1} or greater, for detecting autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering

from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, wherein the interaction of said binding partner with the TSH receptor is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

83. A method of screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with (i) a full length TSH receptor, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor, and (ii) a binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42, under conditions that allow interaction of the TSH receptor with autoantibodies produced in response to the TSH receptor, so as to permit said TSH receptor, or said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to the TSH receptor present in said sample, or said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(c) monitoring the interaction of said TSH receptor, or said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

84. A method according to any of claims 74 to 78 and 83, which further employs one or more competitors that compete in the interaction of said polyclonal antibody, TSH or one or more variants, analogs, derivatives or fragments thereof, or said binding partner or further binding partner for the TSH receptor as respectively defined by said claims and the second molecule of the binding pair as defined in any of claims

74 to 78, or said TSH receptor, or said one or more epitopes thereof or said polypeptide of claim 83.

85. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of said binding pair comprises a binding region with which said binding partner or further binding partner interacts;

(b) means for contacting said sample of body fluid from said subject with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(c) means for monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

86. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of said

binding pair comprises a binding region with which said binding partner or further binding partner interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(b) means for contacting said sample of body fluid from said subject with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(c) means for monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

87. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a human or non-human polyclonal antibody to the TSH receptor and a second molecule of said binding pair comprises a binding region with which said polyclonal antibody interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(b) means for contacting said sample of body fluid from said subject with said one or more pairs of binding molecules so as to permit said second molecule

of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said polyclonal antibody; and

(c) means for monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

88. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises TSH or one or more variants, analogs, derivatives or fragments thereof, and a second molecule of said binding pair comprises a binding region with which said TSH or one or more variants, analogs, derivatives or fragments thereof interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(b) means for contacting said sample of body fluid from said subject with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) TSH or one or more variants, analogs, derivatives or fragments thereof; and

(c) means for monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

89. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner for the TSH receptor which has an affinity for the TSH receptor of 10^{10}molar^{-1} or greater and a second molecule of said binding pair comprises a binding region with which said binding partner interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(b) means for contacting said sample of body fluid from said subject with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said binding partner for the TSH receptor; and

(c) means for monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

90. A kit for screening for autoantibodies to the TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to the TSH receptor, said kit comprising:

(a) a full length TSH receptor, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of the TSH receptor;

(b) a binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42;

(c) means for contacting said sample of body fluid from said subject, said TSH receptor, or said one or more epitopes thereof or said polypeptide, and said binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42, under conditions that allow interaction of the TSH receptor with autoantibodies produced in response to the TSH receptor, so as to permit said TSH receptor, or said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to a TSH receptor present in said sample, or said binding partner for the TSH receptor or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(d) means for monitoring the interaction of said TSH receptor, or said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

91. A kit according to any of claims 85 to 90, which further comprises one or more competitors that compete in the interaction of said polyclonal antibody, TSH or one or more variants, analogs, derivatives or fragments thereof, or said binding partner or further binding partner for the TSH receptor, as respectively defined by said claims, and the second molecule of the binding pair as defined in any of claims 85 to 89, or said TSH receptor, or said one or more epitopes thereof or said polypeptide of claim 90.

92. A method of assaying TSH and related ligands, said method comprising:

(a) providing a sample suspected of containing or containing TSH or related ligands;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of

said binding pair comprises a binding region with which said binding partner interacts;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) TSH or related ligands present in said sample, or (ii) said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(d) monitoring the interaction of said second molecule of said binding pair with TSH or related ligands present in said sample, thereby providing an indication of the presence of TSH or related ligands in said sample.

93. A kit for assaying TSH or related ligands, said kit comprising:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 and a second molecule of said binding pair comprises a binding region with which said binding partner interacts;

(b) means for contacting a sample suspected of containing or containing TSH or related ligands with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) TSH or related ligands present in said sample, or (ii) said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42; and

(c) means for monitoring the interaction of said second molecule of said binding pair with TSH or related ligands present in said sample, thereby providing an indication of the presence of TSH or related ligands in said sample.

94. A method of identifying a further binding partner for the TSH receptor, which further binding partner is capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor according to any of claims 1 to 27, which further binding partner does not comprise TSH, which method comprises:

(a) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner for the TSH receptor according to any of claims 1 to 27 and a second molecule of said binding pair comprises a binding region with which said binding partner interacts;

(b) providing a further binding molecule to be assayed as a potential further binding partner for the TSH receptor which competes for binding to the TSH receptor with said first molecule of said binding pair of (a);

(c) contacting said further binding molecule of (b) with said one or more pairs of binding molecules of (a) so as to permit said second molecule of said binding pair of (a) to interact with either (i) said further binding molecule of (b), or (ii) said first molecule of said binding pair of (a); and

(d) monitoring the interaction of said second molecule of said binding pair of (a) with said further binding molecule of (b), and thereby assessing whether said further binding molecule of (b) competes for binding to the TSH receptor with said first molecule of said binding pair of (a).

95. A kit for identifying a further binding partner for the TSH receptor, which further binding partner is capable of binding to the TSH receptor and which competes for binding to the TSH receptor with a binding partner for the TSH receptor according to any of claims 1 to 27, which further binding partner does not comprise TSH, which kit comprises:

(a) one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a binding partner for the TSH receptor according to

any of claims 1 to 27 and a second molecule of said binding pair comprises a binding region with which said binding partner interacts;

(b) means for contacting said one or more pairs of binding molecules of (a) with a further binding molecule to be assayed as a potential further binding partner for the TSH receptor which competes for binding to the TSH receptor with said first molecule of said binding pair of (a), so as to permit said second molecule of said binding pair of (a) to interact with either (i) said further binding molecule, or (ii) said first molecule of said binding pair of (a); and

(c) means for monitoring the interaction of said second molecule of said binding pair of (a) with said further binding molecule, and thereby assessing whether said further binding molecule competes for binding to the TSH receptor with said first molecule of said binding pair of (a).

96. A process of identifying one or more epitope regions of the TSH receptor, which process comprises contacting a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 with a full length TSH receptor, or one or more fragments thereof, so as to allow interaction of said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 with said full length TSH receptor, or said one or more fragments thereof, and identifying the amino acids of said full length TSH receptor, or said one or more fragments thereof, with which said binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 interacts.

97. One or more anti-idiotypic antibodies generated to a binding region of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42.

98. An anti-idiotypic antibody which is 7E51 IgG prepared according to the Examples.

99. A method of identifying antibody binding sites, which method comprises screening of phage-displayed random libraries with a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42.

100. A binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 for use in therapy.

101. A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42.

102. A pharmaceutical composition comprising a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

103. A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, which binding partner or further binding partner for the TSH receptor stimulates the TSH receptor.

104. Use of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, in the manufacture of a medicament for use in stimulating thyroid tissue, or tissue containing a TSH receptor.

105. Use of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, in the manufacture of a medicament for use in the treatment of thyroid cancer.

106. A method of stimulating thyroid tissue, and / or tissue containing the TSH receptor, which method comprises administering to a patient in need of such stimulation a diagnostically or therapeutically effective amount of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42.

107. In combination a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, together with one or more further agents capable of stimulating thyroid tissue, and / or tissue containing a TSH receptor, for simultaneous, separate or sequential use in stimulating thyroid tissue, and / or tissue containing a TSH receptor.

108. A combination according to claim 107, wherein said one or more further agents comprise recombinant human TSH and / or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

109. A combination according to claim 108, wherein said one or more further agents acts independently of binding to the TSH receptor.

110. A method of treating autoimmune disease associated with an immune reaction to a TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, which binding partner or further binding partner for the TSH receptor inactivates or renders unresponsive the TSH receptor to TSH, TSH receptor autoantibodies or other stimulators.

111. In combination, a binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, together with one or more further agents capable of inactivating or rendering unresponsive tissue containing a TSH receptor to TSH, TSH receptor autoantibodies or other stimulators.

112. A combination according to claim 111, wherein said one or more further agent acts independently of the TSH receptor.

113. A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of a further binding partner for the TSH receptor according to any of claims 28 to 42, whereby administration of said further binding partner substantially inhibits interaction of the TSH receptor with autoantibodies

present in the patient's circulation, wherein said interaction of said autoantibodies and said TSH receptor is responsible for, or is associated with, said autoimmune disease.

114. A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of an anti-idiotypic antibody according to claim 97 or 98, whereby administration of said anti-idiotypic antibody substantially inhibits interaction of the TSH receptor with autoantibodies present in the patient's circulation, wherein said interaction of said autoantibodies and said TSH receptor is responsible for, or is associated with, said autoimmune disease.

115. A method of treating disease of the retro orbital tissues of the eye associated with autoimmunity to the TSH receptor, which method comprises administration to a patient suffering from or susceptible to such disease a therapeutically effective amount of a further binding partner for the TSH receptor according to any of claims 28 to 42.

116. A method of treating disease of the retro orbital tissues of the eye associated with autoimmunity to the TSH receptor, which method comprises administration to a patient suffering from or susceptible to such disease a therapeutically effective amount of an anti-idiotypic antibody according to claim 97 or 98.

117. Use of a further binding partner for the TSH receptor according to any of claims 28 to 42, in the manufacture of a medicament for the treatment of disease of the retro orbital tissues of the eye associated with activation and / or stimulation of the TSH receptor.

118. Use of an anti-idiotypic antibody according to claim 97 or 98, in the manufacture of a medicament for the treatment of disease of the retro orbital tissues of the eye associated with activation and / or stimulation of the TSH receptor.

119. A binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42 for use as a replacement source for patient serum required to contain TSH receptor antibody or antibodies.

120. A binding partner or further binding partner for the TSH receptor according to any of claims 1 to 42, for use in a preparation required to comprise a defined concentration of TSH receptor antibody or antibodies.